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09/740,211	12/18/2000	Linda B. Couto	AVIGEN.003C1	4340

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/740,211	Applicant(s) COUTO ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13,16,17 and 19* is/are rejected.

7)☒ Claim(s) *14-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 8-17 and 19 are pending examination.

Applicant's traversal, the amendment to claim 8 in paper no. 17 is acknowledged and considered.

Priority

The current status of all non-provisional parent applications referenced should be included. Application no. 09/470,618 is US Patent No. 6,200,560 and application no. 09/364,862 is US Patent No. 6,221,349. However, the current status of these applications is not noted on page 1 of the specification.

Specification

The disclosure is objected to because of the following informalities: The description of drawings on page 6. Several Figures have more than one Figure, however the description only indicates that there is one drawing/figure (e.g. Figure 9 indicates that there is only one figure associated with Figure 9, however, there are two figure for Figure 9.). Suggest amending the description of the drawings in the specification to correspond to the number Figures associated with each Figure (e.g. Figure 9 (9A-9B)).

Appropriate correction is required.

Claim Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 14 does not further limit claim 8, which is limited to a B-domain deleted Factor VIII, whereas claim 14 recites SEQ ID NO: 15, which is a full length Factor VIII.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "said tissue-specific promoter" . There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The rejection for Claims 8-10 and 19 under 35 U.S.C. 102(e) as being anticipated by Dwarki is moot in view of applicants' traversal that Dwarki does not teach using a Factor VIII B-domain deleted in the claimed AAV virion.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 8, 9, 10, 11, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Snyder et al. (US 2002/0155580 A1, effective filing date 5/27/98). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with the B-domain deleted (pages 5-12). The promoter in the vector can be tissue specific for the liver. Snyder further teaches preparing the virus particle in a pharmaceutical composition (page 7).

Applicant's arguments with respect to claims 8-11 and 19 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The rejection for Claims 8, 9, 10, 16, 17, and 19 35 U.S.C. 103(a) as being unpatentable over Chiorini et al. (US Patent No. 5,693,531) taken with Simonet (US Patent No. 6,268,212, filed on 1994) is moot in view of applicants' traversal and the amendment to claim 8.

The rejection for Claims 8-13 and 19 under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al. (US Patent No. 6,221,646, effective filing date, 7/31/1997) taken with Almstedt et al. (WO 91/09122) is moot in view of applicants' traversal and the amendment to claim 8.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 10, 16, and 17, are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al. (US 2002/0155580 A1, effective filing date 5/27/98) taken with Simonet (US Patent No. 6,268,212, filed on 1994). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with the B-domain deleted (pages 5-12).

Snyder teaches that the promoter can be tissue specific for the liver (page 4). Snyder further teaches that one of ordinary skill in the art will appreciate that a tissue-specific promoter for use in the AAV vector may be selected from any of the known liver-specific promoters (page 4). However, Snyder does not specifically teach a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter, wherein the liver-specific promoter is selected from either the HNF-3 albumin promoter or the transthyretin (TTR) gene promoter.

However, at the time the invention was made, tissue specific promoter, specifically liver-specific promoters (e.g. TTR or HNF-3 albumin) were well known in the art for use in enhancing liver expression of a transgene using a vector as exemplified by Simonet. Simonet teaches several liver-specific promoters (e.g. HNF-3 albumin or TTR) that could be used in producing a vector comprising a transgene operably linked to a liver-specific promoter (column 3, line 64-column 4, line 12 and abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Simonet to make a pharmaceutical composition comprising a recombinant AAV comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter selected from either HNF-3 albumin or TTR. One of ordinary skill in the art would have motivated to make the claimed composition because factor VIII is expressed in the liver and the promoters TTR and HNF-3 albumin promoters are used to increase gene expression of a vector in the liver.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 8, 10, 16, and 17 have been considered but are moot in view of the new ground(s) of rejection.

Claims 8, 11, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al. (US 2002/0155580 A1, effective filing date 5/27/98) taken with Almstedt et al. (WO 91/09122). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with B-domain deleted (pages 5-12). Snyder teaches that in order to improve expression efficiency of Factor VIII, the Factor VIII cDNA was modified lacking most of the B domain (page 2). However, Snyder does not specifically teach a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a functional Factor VIII, wherein the nucleotide sequence encodes a heavy and a light chain of Factor VIII with the B domain deleted, and wherein said light chain and heavy chain of Factor VIII are operably linked to a junction having Ser-Phe or SEQ ID NO: 15.

However, at the time the invention was made, a recombinant factor VIIII protein comprising a first DNA segment coding for the 90kDa chain and a second DNA segment coding for the 80kDa chain of human factor VIII, wherein the segments were interconnected by a linker DNA segment coding for a linker peptide of 4 to about 100 amino acid residues (having Ser-Phe or encoding claimed SEQ ID NO: 15) was well known in the art as exemplified by Almstedt (abstract). Almstedt further teaches that the DNA sequence can be expressed in recombinant

expression vectors (abstract). In addition, Almstedt teaches that the smallest active form (one heavy chain and one light chain) with a molecular weight of 170kDa could be activated by thrombin to the same extent as the high molecular weight forms and there was an indication that that smaller form has a 50% longer survival time compared to the higher molecular form (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Almstedt to make a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted Factor VIII protein, and wherein said nucleotide sequence further encodes a junction that operably links said heavy and light chain of Factor VIII. One of ordinary skill in the art would have motivated to make the composition because Almstedt teaches that the smaller form of Factor VIII comprising both chains has a 50% longer *in vivo* survival time compared to the higher molecular forms of Factor VIII.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 8, 11, 12, and 13 have been considered but are moot in view of the new ground(s) of rejection.

Claims 14 and 15 are free of the prior art.

Claim 15 is objected to as being dependent upon a rejected base claim (claim 8), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER